Complete Summary

GUIDELINE TITLE

An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia.

BIBLIOGRAPHIC SOURCE(S)

American Society of Hematology. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia. Blood 1999 Sep 1;94(5):1517-36. [108 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic myeloid leukemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review and to document evidence-based benefits and harms of treatment of chronic myeloid leukemia (CML) with busulfan, hydroxyurea, recombinant interferon-alpha, and bone marrow transplantation.

TARGET POPULATION

Patients in the chronic phase of chronic myeloid leukemia.

Chronic myeloid leukemia was considered present only with evidence of the Ph+ chromosome and/or chimeric bcr/abl gene. Excluded were bcr-abl-negative and Ph-negative disease, juvenile chronic myeloid leukemia, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia or hypereosinophilic syndrome, and Ph+ acute leukemia.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Chemotherapy with busulfan and hydroxyurea
2. Recombinant interferon
3. Allogeneic bone marrow transplantation

MAJOR OUTCOMES CONSIDERED

- Treatment efficacy
  - Primary outcome: life expectancy (3-yr, 5-yr survival rates)
  - Intermediate outcomes: hematologic remission, cytogenetic remission
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A computerized literature search of the MEDLINE database, conducted in 1996, sought all publications in which the text words "chronic myelogenous leukemia" appeared in the title or abstract. This search term was not expanded because an initial list of 2,423 citations was retrieved, of which 960 addressed treatments of interest. Two hundred seven articles met criteria for closer inspection.

NUMBER OF SOURCE DOCUMENTS

- 2,423 citations were identified from the searches
- 960 addressed treatments of interest

- 207 met criteria for closer inspection

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Both observational studies and randomized controlled trials were reviewed, but the latter were generally considered a stronger class of evidence. For both categories, the internal validity of studies was judged on the basis of explicit criteria: sample size and statistical power, selection bias, methods for allocation to treatment groups, attrition rate, definition of intervention and outcomes, confounding variables, data collection biases, and statistical methods.

External validity was judged in terms of the patients, treatment protocol, and clinical setting examined in the study.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The designs, results, and limitations of the studies were assembled systematically in evidence tables.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations were evidence-based: this means that treatments could not be recommended unless the evidence met explicit predetermined criteria shown in Table 1 in the guideline document and provided below in the numbered list. When such data were lacking, the panel generally chose not to make recommendations on the basis of indirect evidence (e.g., uncontrolled observational studies) or expert opinion.

1. Recomendations can be made only if there is direct scientific evidence of improved health outcomes (see no. 2), not because a panel member believes there is benefit nor because it is accepted practice in CML care. When such evidence is lacking, the results of the analysis should state: "There is insufficient evidence to make a recommendation."
2. The Analysis will not result in recommendation for one intervention over another unless there is evidence from a controlled study (internal controls) or from dramatic findings in an uncontrolled study that patients treated with that

intervention experience better outcomes (e.g., higher survival) than those treated by the alternative. The outcomes that matter most are those that patients experience (e.g., lengthened survival), not intermediate outcomes for which the linkage to health outcomes is less certain (e.g., cytogenetic remission).

3. When extrapolations of evidence are made from one patient population to another to infer effectiveness, the Analysis should make this explicit and discuss the implications.
4. Claims of proof should be accompanied by full disclosure of the limitations of the evidence.
5. Claims about benefit should clarify the magnitude of benefit, preferably in absolute terms rather than as relative benefit. These claims should be accompanied by a description of potential harms, preferably by estimating the probability of these harms. Confidence intervals should be used to clarify the range of uncertainty about the estimates.
6. When there are complex tradeoffs between benefits and harms such that patients might have different views about the best choice depending on personal preferences, the Analysis should not make categorical recommendations but should instead advise shared decision-making based on the values patients assign to potential outcomes.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recombinant Interferon

1. Based on evidence from randomized controlled trials, patients with good prognostic factors in the early stage of chronic-phase chronic myeloid leukemia should be offered recombinant interferon, perhaps with added chemotherapy (e.g., hydroxyurea or cytarabine) to achieve the highest probability of survival. This recommendation applies to newly diagnosed patients in chronic phase who do not suffer from other serious conditions that limit life expectancy or contraindicate the use of recombinant interferon.

2. Patients considering the aforementioned option should understand the degree to which life expectancy is increased by recombinant interferon in comparison to chemotherapy median of about 20 months on average to determine whether the added benefit is worth the increased risk of adverse effects associated with recombinant interferon and the resulting effect on quality of life (patients who achieve a major cytogenetic response, however, may have a more prolonged survival). Patients should receive complete information about the most serious potential adverse effects of recombinant interferon and their frequency to make an informed choice about its preferability to chemotherapy.
3. In terms of proven survival benefits over hydroxyurea, the evidence from one randomized trial is that monotherapy with recombinant interferon is ineffective. The clinical trials in which recombinant interferon has been shown to be more effective than chemotherapy combined recombinant interferon with other agents (hydroxyurea, busulfan, or cytarabine) and included fewer patients with advanced disease.
4. In clinical trials that did produce improved survival, the starting dose for recombinant interferon was 3 to 5 MU/M2/d. The doses were gradually increased after 2 to 3 weeks to as high as 9 to 12 MU/d or to the maximally tolerated dose to achieve a satisfactory hematologic response (i.e., white blood cell count of 2,000 to 4,000/ÂµL, platelet count approximately 50,000/ÂµL) or until the patient developed signs of toxicity and required dose reduction.
5. There is inadequate evidence from controlled trials to recommend an optimal duration of recombinant interferon therapy. In most trials, complete cytogenetic remissions were noted from 6 to 60 months after recombinant interferon therapy was started. In each study, recombinant interferon was continued until disease progression or toxicity was noted.
6. Based on evidence from a recent randomized controlled trial, adding cytarabine (20 mg/M2/d × 10 d) to recombinant interferon is an option to increase the probability of survival, but the incremental benefit of doing so should be weighed against the increased risk of toxicity associated with this combination.
7. Prolonged survival is most likely when a major or complete cytogenetic response is obtained after recombinant interferon therapy. There is conflicting evidence from controlled trials to determine how long to continue recombinant interferon treatment in patients who have achieved a complete response or, alternatively, who have demonstrated unsatisfactory hematologic or cytogenetic responses. Observational studies suggest that complete cytogenetic remissions tend to require from 6 months to 4 years of therapy. Evidence regarding treatment options for patients who have failed to respond to recombinant interferon was not reviewed by the panel.
8. There is inadequate evidence to set an upper age limit for considering recombinant interferon therapy for chronic myeloid leukemia. In the clinical trials that instituted an age-cutoff, patients were excluded if they were over the age of 70 to 75 years.
9. Based on proven effects on survival, there is inadequate evidence from controlled trials to recommend recombinant interferon over chemotherapy for patients in advanced chronic phase, including those with symptomatic disease or physical findings (e.g., unexplained fatigue, weight loss, fever, progressive organomegaly, treatment-resistant leukocytosis, thrombocytosis, >10% blasts and promyelocytes in the differential count, extramedullary manifestations).

10. For those patients who prefer conventional chemotherapy rather than recombinant interferon, evidence from one randomized controlled trial (and several observational studies) supports the use of hydroxyurea rather than busulfan as the agent more likely to improve survival and less likely to produce serious toxicity. Hydroxyurea is a reasonable treatment option for patients who understand its reduced survival benefits in comparison to recombinant interferon but prefer its less severe toxicity profile.

Allogeneic Bone Marrow Transplant

1. If physicians and patients require evidence of benefit from bone marrow transplantation from randomized controlled studies to determine treatment preferences, then evidence to make such a recommendation is lacking. Randomized prospective studies with internal controls have not been conducted to show whether allogeneic bone marrow transplantation, either as first-line treatment or after initial treatment with chemotherapy or recombinant interferon, achieves longer survival than nontransplant therapy. Uncontrolled observational studies do report higher long-term survival rates with allogeneic bone marrow transplantation after chemotherapy compared with those typically seen in patients treated only with nontransplant approaches, and bone marrow transplantation appears to offer a greater chance of long-term remission. It is uncertain to what extent these results are due to selection biases and the analytic methods used. Moreover, whether they can be generalized to normal practice conditions is uncertain. Further, bone marrow transplantation is associated with a high risk of immediate complications and transplant-related mortality that can offset the benefits of treatment, especially in the short term. For physicians and patients who are comfortable accepting evidence from uncontrolled observational studies which suggest that allogeneic bone marrow transplantation is more effective than nontransplant approaches and who are interested in considering transplantation, the following recommendations are offered:
2. Allogeneic bone marrow transplantation is an option if the patient has a suitable human leukocyte antigen-matched donor and an acceptable health status to tolerate the procedure.
3. Based on information provided, a patient must fully understand the tradeoff between potential long-term benefits and the more immediate risks of transplant-related complications and mortality. Depending on personal priorities and life plans, the patient should decide whether the potential increase in life expectancy is worth this risk. The patient should understand how his or her age, duration of illness, human leukocyte antigen match with the donor, and the experience of the transplant center may modify standard outcome estimates. Decisions to delay the procedure or, if a related donor is unavailable, to use a matched unrelated donor, should be made with a clear understanding of how these choices may reduce the chances of success.
4. Bone marrow transplantation should preferably be offered to patients within 1 to 2 years of diagnosis to achieve the greatest likelihood of success (according to evidence from uncontrolled observational studies). Patients with adverse prognostic factors (reflected by a high Sokal score) should understand that their chances of success with recombinant interferon are reduced and that early bone marrow transplantation may be a more compelling option. For patients who have had chronic myeloid leukemia for more than 1 year and for those who are considering delaying bone marrow

transplantation until more than 1 year from diagnosis, a decision is required of whether the decreased likelihood of benefit justifies the risk of transplant.

5. Younger patients are most likely to benefit from allogeneic bone marrow transplantation. Bone marrow transplantation is also more successful if the donor is a human leukocyte antigen-matched sibling or other relative according to evidence from uncontrolled observational studies. Results at most centers are inferior when the transplant is performed with marrow from "matched" unrelated donors, but outcomes vary depending on patient selection, transplant methodology, typing techniques, the expertise of the participating center, and the definition of accelerated- and blast-phase disease. Although the tradeoff between benefits and harms from bone marrow transplantation narrows with advancing patient age and although there is virtually no experience with bone marrow transplantation beyond age 65 years, there is inadequate evidence to determine an upper age limit beyond which bone marrow transplantation should not be offered.
6. Patients receiving chemotherapy before allogeneic bone marrow transplantation appear less likely to benefit from transplant if they have been treated with busulfan according to evidence from uncontrolled observational studies. If the patient chooses early bone marrow transplantation, there is little evidence to determine the possible benefit of prior cytoreduction with hydroxyurea or recombinant interferon. There is observational evidence that prior treatment with recombinant interferon does not compromise the results of matched-related transplants, but its effect on bone marrow transplantation with matched unrelated donors, based on a published study, appears deleterious. It is also unclear whether the patient's hematologic or cytogenetic response to recombinant interferon can reliably predict the success of allogeneic bone marrow transplantation.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by controlled and uncontrolled observational studies, randomized controlled trials, and letters to the editor containing primary data.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Hydroxyurea, Busulfan

The superiority of hyrdoxyurea was established after a randomized controlled trial compared hydroxyurea and busulfan and showed that median survival was significantly shorter for busulfan-treated patients than for those treated with hydroxyurea (45 versus 48 months) (P = 0.008). The 5-year survival rates were

32% and 44%, respectively. A recent meta-analysis of 5 other trials also supports a survival advantage for hydroxyurea over busulfan.

Recombinant Interferon

The most compelling evidence that recombinant interferon is more efficacious than chemotherapy comes from four (4) prospective, randomized studies showing a statistically significant improvement in survival rates in patients receiving recombinant interferon. Five-year survival rates in these randomized controlled trials were 50% to 59% for patients receiving interferon and 29% to 44% for patients receiving busulfan or hydroxyurea.

The bulk of the evidence that recombinant interferon improves survival comes from trials in which it is combined with other drugs. There is no direct evidence (from randomized controlled trials) that recombinant interferon has a greater impact on survival than hydroxyurea for chronic-phase patients who are in the later stages of chronic phase or who are sicker (eg, more than 1 year from diagnosis, or more than 10% to 30% blasts in peripheral blood). The single trial in which recombinant interferon was used as monotherapy did not show a survival benefit. Adding cytarabine to recombinant interferon appears to add further survival benefit but also increases toxicity.

These benefits must be weighed against the adverse effects of the drug before judgments can be made about whether the tradeoff is worthwhile.

Allogeneic Bone Marrow Transplantation

The efficacy of allogeneic bone marrow transplantation in the treatment of chronic-phase chronic myeloid leukemia has been evaluated in a number of uncontrolled observational studies and several prospective studies. Projected actuarial 3-year to 5-year survival rates in these studies range from 38% to 80%, with the higher values reported by experienced centers. Most studies report values around 50% to 60% and slightly lower probabilities for disease-free survival. Reported relapse rates within 3 to 5 years are often less than 20%. Projected survival curves appear to plateau (or taper more slowly) after 3 to 7 years, suggesting that allogeneic bone marrow transplantation offers eligible chronic-phase patients (especially young adults with a genetically human leukocyte antigen-identical sibling donor) a prospect for cure.

Subgroups Most Likely to Benefit:

Recombinant Interferon

- Chronic-phase patients with favorable features: no or minimal prior treatment, relatively normal hemoglobin levels and platelet counts, less than 10% blasts in the blood, and beginning treatment especially within 6 months of diagnosis when recombinant interferon is coupled with other agents (hydroxyurea or cytarabine). During early chronic phase, the treatment advantage of recombinant interferon over chemotherapy is observed with varying magnitude in patients in each Sokal score (risk) category.

- Newly diagnosed patients in chronic phase of chronic myeloid leukemia who do not suffer from other serious conditions that limit life expectancy or contraindicate the use of recombinant interferon

Allogeneic Bone Marrow Transplantation

- Chronic-phase patients who have suitable human leukocyte antigen-matched donors and an acceptable health status to tolerate the procedure. Bone marrow transplantation is more successful if the donor is an human leukocyte antigen-matched sibling or other relative.
- Chronic-phase patients in their first or second year after diagnosis: most data suggest that instituting bone marrow transplantation within 1 to 2 years of diagnosis results in higher survival rates than bone marrow transplantation after 2 years.
- Younger chronic-phase patients: most studies suggest that patients under age 30 years have higher overall and disease-free survival and lower transplant-related mortality than patients over age 30.

POTENTIAL HARMS

Recombinant Interferon

Evidence regarding the adverse effects of recombinant interferon in chronic myeloid leukemia comes mainly from retrospective observational studies. Reported complication rates vary widely owing to differences in patient selection and case mix, thoroughness of investigators in measuring side effects, definition of complications (eg, whether acute, subacute or chronic, mild or severe), sample size, dose and duration of recombinant interferon, and length of treatment and follow-up.

In general, however, the evidence supports the clinical observation that toxicity is more common with recombinant interferon than with busulfan or hydroxyurea. Virtually all patients receiving recombinant interferon experience some constitutional side effects (refer to Table 5 in the original guideline for details), and discontinuation of treatment due to toxicity is necessary for 4% to 18% of patients compared with 1% of those receiving hydroxyurea. One observational study reported that patients received only 60% of the target dose owing to side effects. Acute side effects are generally mild to moderate and include flulike symptoms such as fever, chills, and malaise. A wide constellation of other more severe acute reactions and chronic complications can occur. Overall, the mechanisms underlying the toxic effects are not well understood, but the incidence of adverse effects is usually dose and duration dependent.

Allogeneic Bone Marrow Transplantation

Assuming that bone marrow transplantation is proven to increase the chances of survival in comparison to recombinant interferon, the magnitude of the incremental increase in benefit must be weighed against the potential of serious harms and even death that may accompany the procedure, especially in the short term.

- Death rate. The reported probability that the patient will die as a result of bone marrow transplantation (transplant-related mortality) ranges from 20% to 41%. Studies that included chronic-phase patients treated in the 1980s or those who received marrow from mismatched or unrelated donors report rates as high as 53% to 68% in certain subgroups. On the other hand, one center has reported rates as low as 15% among chronic-phase patients treated in recent years with marrow from matched siblings and receiving modern regimens for the prevention of opportunistic infections and graft-versus-host disease.
- Preparatory regimen. The preparatory regimen produces toxic effects in virtually all patients. Severe oral mucositis is reported in about half of chronic-phase patients.
- Graft-versus-host disease. Bone marrow transplantation is often followed by graft-versus-host disease, opportunistic infections, or other complications. Between 8% and 63% of chronic-phase patients experience grade II-IV acute graft-versus-host disease, a possible determinant of survival and the cause of death for 2% to 13% of patients undergoing bone marrow transplantation. (Some studies suggest that graft-versus-host disease has an antileukemic effect and improves survival.) The rates for chronic graft-versus-host disease are 4% to 75%, with 8% to 10% mortality. Similar findings have been reported in studies that included patients with both chronic myeloid leukemia and other leukemias. Higher rates of graft-versus-host disease tend to be reported by studies which included chronic-phase patients treated in the 1980s or those who received marrow from mismatched or unrelated donors. Among chronic-phase patients receiving marrow from matched siblings and modern methods for graft-versus-host disease prevention, reported incidence rates for acute and chronic graft-versus-host disease are 35% or lower.
- Interstitial pneumonitis, veno-occlusive disease, and secondary malignancies. Between 4% and 32% of chronic-phase patients undergoing bone marrow transplantation die of interstitial pneumonitis, 3% to 24% die of other infections, and 1% to 4% die of hepatic veno-occlusive disease. Long-term complications can include second malignancies, cataracts, and infertility.

Subgroups Most Likely to be Harmed:

Allogeneic Bone Marrow Transplant

- Recipients of bone marrow from a human leukocyte antigen-matched unrelated donor generally have lower survival and are more likely to develop graft-versus-host disease than those who receive a marrow transplant from a human leukocyte antigen-matched sibling or other relative. At one experienced center, however, survival rates after transplantation of matched unrelated donors are approaching those of matched siblings. Moreover, modern methods of genomic typing of class I human leukocyte antigen alleles adds substantially to the success of transplantation from unrelated donors.
- Patients who receive busulfan before bone marrow transplantation may have lower survival rates than those who receive hydroxyurea.
- T-cell depletion reduces the risk of graft-versus-host disease, but it increases the risk of relapse and lowers survival.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The recommendations contained in this analysis describe a range of approaches to the management of chronic myeloid leukemia. These recommendations are not intended to serve as inflexible rules, and they are not inclusive of all proper methods of care or other methods of care that may achieve similar results. Adherence to the recommendations will not ensure a successful outcome in every case. The ultimate judgement regarding the care of a particular patient should be made by the physician in light of the clinical data and circumstances presented by the patient and the treatment options available.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Society of Hematology. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia. Blood 1999 Sep 1;94(5):1517-36. [108 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Sep 1

GUIDELINE DEVELOPER(S)

American Society of Hematology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Hematology

GUIDELINE COMMITTEE

Expert Panel on Chronic Myeloid Leukemia (CML)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The 12-member panel included hematologists and oncologists from the United States, England, France, Germany, and Italy with research expertise in the treatment of chronic myeloid leukemia (CML), practicing hematologists from the United States, a biostatistician, and a practice guidelines methodologist. One of the panelists was also a designated representative of the American Society of Clinical Oncology.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available to members and subscribers from www.bloodjournal.org.

Print copies: Available from the American Society of Hematology, 1200 19th Street, N.W., Third Floor, Washington, DC 20036-2422.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 11, 2000. The information was verified by the guideline developer on December 12, 2000.

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